Diabetic Dyslipidemia

A Science Writer's Guide

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Overview

Diabetic dyslipidemia: it's *not* just high cholesterol. It's a triad of lipid abnormalities, typically seen in people with type 2 diabetes.

Almost **20 million Americans have diabetes, of whom 5.9 million remain undiagnosed,** and type 2 diabetes may account for 90-95 percent of all diagnosed cases.

Most people with diabetes have diabetic dyslipidemia; it's part of what raises their risk of cardiovascular disease (CVD). Dyslipidemia is part of the metabolic syndrome, which increases the risk of CVD. Obesity is an underlying component of this syndrome, too.

Cardiovascular disease (CVD), including heart attack and stroke, is the leading cause of diabetes-related death.

Type 2 diabetes typically appears in midlife and is strongly associated with obesity. Indeed, obesity and physical inactivity are two risk factors for type 2 diabetes. However, now, as obesity reaches epidemic proportions in children, a growing number of children and adolescents are developing type 2 diabetes. These youngsters are likely to encounter the same serious complications of diabetes including heart disease and stroke, perhaps even in young adulthood. The crisis is here, now.

The healthcare community urgently needs to target diabetes and diabetic dyslipidemia in a coordinated manner to avert further morbidity and mortality.

Inside this guide, which was developed by Takeda Pharmaceuticals North America, Inc., you'll find more on every one of these statements, including references. If you want even more information, we can provide leads to interviews with experts.

Introduction: Statistics

1. Introduction

Statistics

According to the American Heart Association (AHA), almost 20 million Americans have diabetes, of whom 5.9 million remain undiagnosed. Many people with type 2 diabetes are not even aware they have the disease, although they may have already developed associated complications. In addition to these complications, medical conditions associated with this disease include high blood pressure and cholesterol, which may lead to heart disease and stroke.

CVD is the leading cause of death for individuals with diabetes. People with diabetes are at high risk for having a heart attack or stroke. In fact, physicians believe that people with diabetes are at higher risk for a cardiovascular event than those who smoke, have cholesterol or high blood pressure, or are obese.

What percentage of people with diabetes die of CVD? The number cited by the National Institutes of Health is 65 percent.

The rate of deaths due to heart disease in America has been dropping in recent decades. This rate, however, has not dropped as much for people with diabetes as for the rest of the population.

Although there has been a reduction in the incidence of CVD events, such as heart attack, stroke and death among people with diabetes over the past 50 years, the absolute risk of such events is still twice as great in those with diabetes compared to the general population, according to a survey of the Framingham Heart Study population.

The National Health and Nutritional Examination Survey concluded that, since 1971, deaths from heart disease in women with diabetes have increased 23 percent, compared to a 27 percent decrease in women without diabetes – and that such deaths in men with diabetes have decreased only 13 percent compared to a 36 percent decrease in men without diabetes.

According to the U.S. Centers for Disease Control, 70-97 percent of people with type 2 diabetes have diabetic dyslipidemia, a condition associated with an increased risk for heart disease.

According to a recent American Diabetes Association position statement, “Aggressive therapy of diabetic dyslipidemia will reduce the risk of cardiovascular disease in patients with diabetes.”

More than 60 million Americans have insulin resistance, a condition in which the body cannot use insulin efficiently.

To compensate, the pancreas releases more and more insulin to try to keep blood sugar levels normal. Gradually, however, the insulin-producing cells of the pancreas become defective and decrease in number. Blood sugar levels then rise, resulting in full-blown diabetes. About 9 out of 10 patients with type 2 diabetes have insulin resistance.

The World Health Organization estimates that 60 percent of the 56 million deaths worldwide in 2001 were caused by such obesity-related illnesses as heart disease and type 2 diabetes.

A growing number of children and adolescents are developing type 2 diabetes, a form of diabetes that was once generally diagnosed among adults. Obesity in childhood lays the metabolic groundwork for adult cardiovascular disease, as many overweight children will become overweight adults.

As obesity reaches epidemic proportions in developed countries, it is expected that pre-teens will more frequently develop type 2 diabetes – a disease usually seen more often in those over 45 and overweight. In a recent multi-state study of 8th graders, 49.3 percent were overweight, 13.9 percent were defined as having metabolic syndrome, 40.2 percent had pre-diabetes and 0.4 percent had diabetes. A significant number also had lipid problems and elevated systolic or diastolic blood pressure levels. "Our survey of 1,700 8th-grade children in Texas, North Carolina and California found that more than half had one or more problems, such as being overweight or having cholesterol, blood pressure or blood glucose abnormalities, that place them at high risk for diabetes and premature cardiovascular disease unless improved nutrition and increased physical activity reverse their risks," reported Francine Kaufman, MD, head of the Center for Diabetes and Endocrinology, Children's Hospital of Los Angeles, and Chair of the Studies to Prevent Pediatric Type 2 Diabetes Study Group (STOPP-T2D), at the American Diabetes Association 2004 Scientific Sessions.

An estimated 36.3 million U.S. adults have the metabolic syndrome.

1 in 3 Americans born in 2000 will develop diabetes.

That's the estimated lifetime risk of developing diabetes for people born in 2000 – 33 percent for males and 39 percent for females – with even higher rates for Hispanics, according to a U.S. Centers for Disease Control and Prevention (CDC) report. Might diabetes become a "standard part of aging"? How will that impact our society?

Putting their money where their values are: Consider that the American Diabetes Association (ADA) recently launched a professional journal called *DOC News*. According to its editor, *DOC* is an "acronym for one of the most important public health crises in the world: the triad of diabetes, obesity, and cardiovascular disease." It's a singular statistic: one whole new journal.

Lipids (Blood Fats)

2. Lipids/Blood Fats

Lipids, also known as blood fats, include cholesterol, triglycerides and lipoproteins, which are molecules of fat and cholesterol linked to protein. They include:

- **Low-density lipoprotein cholesterol (LDL-C)** – the so-called "bad" cholesterol;
- **High-density lipoprotein cholesterol (HDL-C)** – the so-called "good" cholesterol;
- **Very low-density lipoprotein cholesterol (VLDL-C)** – mostly composed of cholesterol; considered by many as another form of "bad" cholesterol.

Is diabetic dyslipidemia the same thing as elevated cholesterol? No.

Diabetic dyslipidemia refers to a specific profile, a triad of lipid abnormalities. More on that in a moment.

First, it might be helpful to define a number of conditions with names that seem interchangeable but that are actually quite different, leading to a full definition of our subject.

- ***Hypercholesterolemia*** refers generally to elevated cholesterol levels in the blood.
- ***Hypertriglyceridemia*** refers specifically to elevated levels of triglyceride in the blood.
- ***Hyperlipidemia*** refers to elevated levels of fat or cholesterol in the blood and includes, for example, hypercholesterolemia and hypertriglyceridemia.
- ***Dyslipidemia*** refers to abnormal levels of lipids in the blood.
- ***Diabetic dyslipidemia*** refers to a particular dyslipidemia, a profile characterized by a cluster of abnormalities occurring together:
  - Elevated triglycerides,
  - Reduced levels of HDL-C,
  - Normal or elevated levels of total cholesterol and LDL-C,
  - A shift toward smaller and denser LDL-C particles.

About Diabetes

3. About Diabetes

Types of Diabetes

Before beginning to discuss diabetic dyslipidemia, here's a brief review of diabetes:

Type 1 diabetes is a chronic (lifelong) disease that occurs when the pancreas produces too little insulin to regulate blood glucose (sugar) levels appropriately. Insulin is necessary for the body to be able to use glucose. Glucose is the basic fuel for the cells in the body, and insulin takes the glucose from the blood into the cells. Type 1 diabetes can occur at any age, but it usually starts in people younger than 30.

Type 2 diabetes is a progressive disease that develops when the body does not produce enough insulin and does not efficiently use the insulin it does produce (a phenomenon known as insulin resistance). Type 2 diabetes, the most common form of diabetes, usually appears in adults, often in middle age. In a mild form, type 2 diabetes can go undetected for many years, although untreated diabetes can lead to many serious medical problems, including cardiovascular disease.

Pre-diabetes is a condition in which blood glucose levels are higher than normal but not yet in the diabetic range. The medical terms for pre-diabetes are impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), depending on the type of test used to diagnose it.

Note: In this science writer's guide, we are primarily discussing type 2 diabetes, because diabetic dyslipidemia is a commonly observed condition in this population. However, we will occasionally refer to pre-diabetes because it is associated with an increased risk of developing type 2 diabetes.

Symptoms

The most common symptoms of diabetes are:

- frequent urination
- excessive thirst
- extreme hunger
- unusual weight loss
- increased fatigue
- irritability
- blurry vision

Diagnosis

Diabetes can be diagnosed by the physician in one of three ways.

1. Symptoms of diabetes plus a "casual" blood test finding of glucose levels of ≥200 mg/dL. Casual is defined as any time of day without regard to time since last meal.
2. A "fasting" blood glucose (FPG) test finding of glucose levels of ≥126 mg/dL. Fasting is defined as no caloric intake for at least 8 hours.
3. An oral glucose tolerance test (OGTT) finding of glucose levels ≥200 mg/dL. For this test, a person's blood glucose is measured after a fast and 2 hours after drinking a glucose-rich beverage.

Other Blood Tests

There are two more important blood tests done in diabetes by patients and physicians.

At home, patients do **s**elf-**m**onitoring of their **b**lood **g**lucose (SMBG) each day or a few times a week. The most common method involves pricking a finger with a lancet device to obtain a small blood sample, which is then collected onto a reagent strip and the glucose concentration is determined by inserting the strip into a reflectance photometer for an automated reading. The test results are then recorded into a logbook or stored in the glucose meter's electronic memory. Using this test, people with diabetes can be taught to use their results to correct any deviations out of a desired target range by changing their carbohydrate intake, exercising or using more or less insulin.

In the doctor's office, a lab technician is likely to do a glycated hemoglobin test – this is also called a hemoglobin A1C test. This test is done by drawing a sample of blood from a vein in a patient's arm, which is then sent to the lab for analysis. This measures the average blood sugar level for the two-to three-month period before the test, which helps the doctor determine how well a person is managing his or her blood glucose. How often this test is done depends on the type of diabetes and how well the person is managing his or her blood glucose; it may range from twice to four times a year.

Glucose control – just the first step

Clearly, maintaining blood glucose levels is a daily challenge for people with diabetes. It is especially important to control blood glucose to prevent or delay the onset of many serious life-threatening health complications. As noted previously, cardiovascular disease is one of the major risk factors for people with diabetes. According to the former president of the ADA, "Diabetes management requires equal attention to control of blood glucose, cholesterol, blood pressure and other cardiovascular risk factors."

Who treats diabetes?

Lots of different types of doctors, other health professionals, and the patients themselves.

The patient is the most important member of the healthcare team. Patients are the ones who actually do the exercise, make and eat the foods on a meal plan, take the medicine or inject the insulin, check their blood glucose levels and keep track of the results. Most of all, the patient is the first to notice any problems, so the healthcare team depends on the patient to talk to them openly so they can provide the best care.

Then there's the primary care physician (PCP) or family practice doctor. The PCP is who you see for general checkups and when you get sick. Some people with diabetes also consult with an endocrinologist, who is a doctor with special training (and usually certification) in diseases such as diabetes.

In addition, people with diabetes may need guidance from a nurse educator with special training in diabetes, who can help a person learn the day-to-day aspects of diabetes self-care. Then there are registered dietitians who can help determine your food needs based on your health goals. Finally, a patient might also want to consult with mental health professionals, who can help with the emotional side of living with diabetes, and/or an exercise physiologist, who can help with the exercise programs that play a major role in diabetes care.

Further, since diabetes carries an increased risk for heart attack and stroke and complications related to poor circulation, the patient may need to add other members to the healthcare team as his or her healthcare needs change.

Complications

Excess glucose in the blood (rather than in the cells) causes two problems: first, the cells may be starved for energy, and second, over time high blood glucose levels may hurt the eyes, kidneys, nerves or heart.

Consider the ***complications*** of diabetes:

- **Microvascular complications** are those that affect small blood vessels such as those found in the eyes and kidneys.
- **Macrovascular complications** are those that affect large blood vessels such as those found in the heart, which may include coronary heart disease and/or stroke.

Treatment

Control of blood glucose levels (glycemic control) is fundamental to the management of diabetes. Several long-term prospective randomized clinical trials, such as the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS), have shown that intensive glycemic control is associated with sustained decreased rates of retinopathy, nephropathy and neuropathy.

The potential of intensive glycemic control to reduce CVD in patients with diabetes is also supported by the DCCT/EDIC and by other epidemiological studies; and a recent meta-analysis supports that chronic hyperglycemia increases the risk for CVD in patients with diabetes.

A complete discussion of treatment is beyond the scope of this guide, but here are the highlights of factors that affect your glucose levels:

Nutrition - Food raises your blood sugar level; therefore, what and how much you eat, and the time of day you eat it, also affect your blood sugar level.

Exercise and Physical Activity - In general, the more active you are, the lower your blood glucose. Physical activity causes glucose to be transported to your cells, where it's used for energy, thereby lowering the levels in your blood. Even exercises such as walking or jogging can help improve your blood glucose.

Medications - Insulin and oral diabetes medications deliberately work to lower your blood glucose. But medications you take for other conditions may affect glucose levels. If you need to take certain high blood pressure medications, your doctor will likely make changes in your diabetes treatment.

Cardiovascular Disease (CVD) in Diabetes

Cardiovascular Disease
(CVD) in Diabetes

4. Cardiovascular Disease (CVD) in Diabetes

What causes a heart attack?

A heart attack, or myocardial infarction, occurs when the blood supply to the heart is severely reduced or stopped. This is usually caused by the buildup of plaque (deposits of fat-like substances) in the arteries, also known as atherosclerosis, which can be the result of excess LDL-C, or "bad," cholesterol circulating in the blood. Therefore, a high level of LDL-C reflects an increased risk of cardiovascular disease. In fact, one study, the Multiple Risk Factor Intervention Trial (MRFIT), showed that among individuals with diabetes and high cholesterol, death rates are much higher than for people without diabetes with the same concentration of cholesterol.

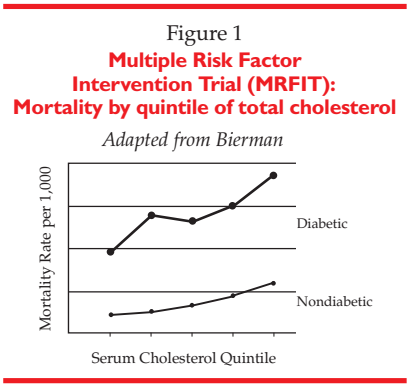


Figure 1. MRFIT: Mortality by Quintile of Cholesterol

Further, people with diabetes tend to have LDL-C particles that stick to arteries and damage their walls more easily. By virtue of their size, the smaller, denser LDL-C particles seen in diabetics more easily permeate the walls of arteries and bind more avidly to the underlying connective tissue than larger, less-dense particles.

The progression of an atherosclerotic plaque is shown below:

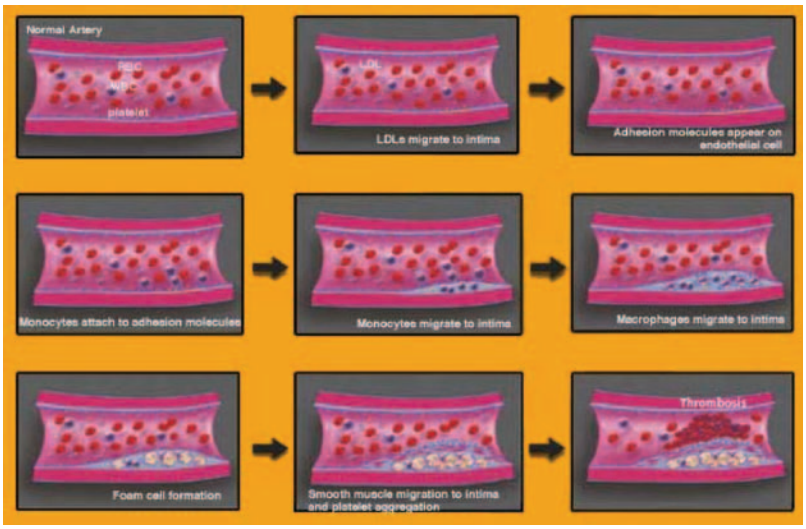


Figure 2. The Progression of Cardiovascular Disease

But today we know that the path to a heart attack starts much earlier. Indeed, a whole host of potentially causative factors or risk factors associated with CVD are frequently observed in people with diabetes. One view of the interplay of these factors was published recently in *Endocrine Reviews*:

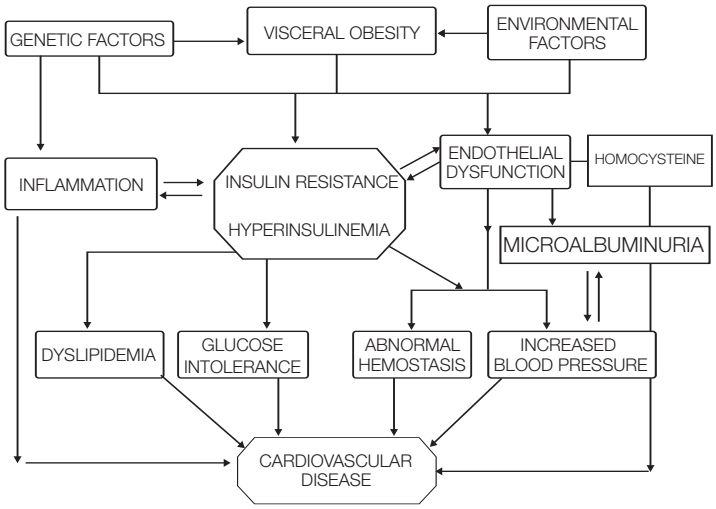


Figure 3. Interaction of CVD Risk Factors in Diabetes

Adapted from: Fonseca V, Desouza S, Asnani S, Jialal I. Nontraditional risk factors for cardiovascular disease in diabetes. Endrocrine Reviews. *2004;25:153-175.*

Based on the chart, one path of risk factors is as follows:

- obesity leading to...
- insulin resistance leading to...
- glucose intolerance (such as pre-diabetes or actual diabetes)...and other complications such as hypertension and dyslipidemia...and eventually...
- cardiovascular disease.

Over on the left is another box marked “inflammation,” which is the process by which the body responds to injury. It has been theorized that inflammation is important in atherosclerosis, the process in which plaque builds up in the lining of the arteries.

C-reactive protein (CRP) is a protein found in the blood that increases during the inflammation process. Therefore, testing for CRP levels may be a new way to assess cardiovascular disease risk. A study published in the *New England Journal of Medicine* randomized 3,745 patients with acute coronary syndromes to 80 mg atorvastatin or 40 mg pravastatin and monitored them for recurrent heart attacks or death from coronary causes. The result was that “patients who have low CRP levels after statin therapy have better clinical outcomes than those with higher CRP levels, regardless of the resultant level of LDL-C. Strategies to lower cardiovascular risk with statins should include monitoring CRP as well as cholesterol.”

In conclusion, diabetes is increasingly recognized as an independent risk factor for cardiovascular disease. Aggressive management (including diet, exercise and pharmacological approaches to normalize blood glucose and blood lipid levels and blood pressure) is urgently recommended in guidelines from the National Diabetes Education Program, which is a program sponsored in part by the National Institutes of Health to improve treatment and outcomes for people with diabetes.

Insulin Resistance

Insulin Resistance

5. Insulin Resistance

Insulin is a critically important hormone that helps the body use food. When food is ingested, the body breaks it down into glucose, which is ultimately used for energy. Insulin acts as a key, unlocking the body's cells and enabling glucose to enter and provide fuel and energy. Glucose is the body's main fuel. Insulin is produced by the beta cells in the pancreas.

Insulin Resistance

Insulin resistance is considered a core metabolic dysfunction of type 2 diabetes. It occurs when the body cannot use insulin efficiently, thereby prohibiting the body from self-regulating the process of turning food into energy. When this occurs, the cells begin to starve, and blood glucose begins to rise to unhealthy levels.

When the pancreas detects an excessive amount of glucose in the blood, it reacts by producing extra insulin. Eventually, the pancreas gets exhausted and can no longer keep up. Therefore, blood glucose remains elevated beyond a normal level, leading to a diagnosis of diabetes.

Insulin resistance typically begins before diabetes is diagnosed and continues to progress, making it difficult to reach target blood glucose levels. It is a core metabolic dysfunction associated with both type 2 diabetes and an increased risk for heart disease and stroke. In addition, it is linked to blood lipid imbalances. More on that later.

What causes insulin resistance? Who gets it?

There are several risk factors associated with insulin resistance:

- Obesity, particularly women with a waist measure over 35 inches, or men with a waist measure over 40 inches
- Physical inactivity
- Genetics
- Polycystic ovary syndrome
- Age 45+
- High blood pressure
- Low HDL (good) cholesterol levels
- High levels of a fat called triglycerides in the blood

About 60 million Americans have insulin resistance, and 25 percent of those will develop type 2 diabetes.

How is it diagnosed?

Currently, there is no commonly used test to diagnose insulin resistance. Therefore, a clinician will check for the above risk factors to ascertain whether a patient is insulin resistant. If risk factors are present, a blood test should be given to check blood glucose levels to see if a diagnosis of diabetes or pre-diabetes could be made.

Diabetic Dyslipidemia

6. Diabetic Dyslipidemia

Dyslipidemia (irregularity of the lipid profile) occurs both in people with diabetes and in people without diabetes. The specific abnormalities in the lipoprotein pattern characteristic of diabetic dyslipidemia appear to add excess risk for diabetes patients. That diabetic dyslipidemia pattern is:

- Elevated triglycerides,
- Reduced levels of HDL-C,
- Normal *or* elevated levels of total and LDL-C,
- A shift toward smaller and denser LDL-C particles.

The goal of therapy is to have all lipoproteins or lipid parameters in the desirable range. Therefore, strategies may be considered that will improve all lipid parameters – LDL-C, HDL-C, triglycerides, and LDL-C particle size. (See section VIII on "Integrated Drug Therapy.")

While elevated serum triglyceride levels alone are considered a major risk factor for cardiovascular disease, they are generally accepted as a marker for other risk factors, particularly small LDL-cholesterol particles and low levels of HDL cholesterol. Nevertheless, the National Cholesterol Education Program's Adult Treatment Panel III (ATP III) Report gives increased weight to elevated triglycerides in cholesterol management in two ways. ATP III classifies non-HDL cholesterol as a secondary target in therapy when triglycerides are high, and as a marker for other lipid and non-lipid risk factors for the metabolic syndrome.

What is the evidence for the role of diabetes and dyslipidemia in heart disease?

There is an association between dyslipidemia and heart disease, as well as diabetes and CVD. The role of elevated LDL-C as a risk factor for CVD in the general population is well-documented, and it applies to people with diabetes as well. However, people with diabetic dyslipidemia often do not have elevated LDL-C. Some observational studies suggest that low HDL-C is an important risk factor for CVD; for studies in which total cholesterol and triglycerides were measured, triglycerides were often a stronger predictor. Therefore, once LDL-C levels have been lowered, attention should be given to treatment of hypertriglyceridemia and low HDL-C.

ATP III noted that "A low HDL-C level is strongly and inversely associated with risk for CHD," and that "Elevated serum triglycerides are associated with increased risk for CHD." It was recommended that "Greater emphasis be placed on elevated triglycerides as a marker for increased risk for CHD."

In its National Diabetes Fact Sheet, the American Diabetes Association notes that "Improved control of cholesterol and lipids (for example, HDL-C, LDL-C, and triglycerides) can reduce cardiovascular complications by 20 percent to 50 percent." Of course, the proof is in the pudding: does CVD go down when you treat dyslipidemia? Clinical trials suggest it does.

Following is a sampling of frequently noted studies providing evidence for the role of dyslipidemia in heart disease.

Epidemiological studies of dyslipidemia in the general population, as well as in those with diabetes

- The **Framingham Heart Study** began following 5,209 adults in that city in Massachusetts in 1948 to see who got heart disease and try to assess what was different about them. Even the first report, based on four years of surveillance, showed that those with the highest HDL-C levels had the lowest levels of coronary heart disease (CHD). By 1986, when those participants were aged 49 to 82 years and had been followed up for 12 years, the relationship between the HDL-C level and subsequent incidence of CHD had not appreciably changed. Study participants at the 80th percentile of HDL-C were found to have half the risk of CHD developing when compared with subjects at the 20th percentile of HDL-C.
- The **Prospective Cardiovascular Munster Study (PROCAM)** was a large prospective epidemiological study of coronary heart disease risk markers in Europe. It found high triglyceride levels were much more common among men (18.6 percent) than women (4.2 percent), although prevalence increased with age in women and remained nearly constant at about 20 percent in men after age 35. A strong negative correlation between triglycerides and HDL-C was found. A sub-analysis followed 4,474 men, aged 40-64, for an average of four years. Although triglycerides were not identified as an independent risk factor in this study, they were found to be an additional risk factor for CHD, when excessive triglycerides coincided with a high ratio of plasma cholesterol to HDL-C and with low LDL-C values.
- The **Atherosclerosis Risk in Communities Study (ARIC)** has been following 12,089 middle-aged people, and they have recently been assessed to determine the magnitude of the association between the National Cholesterol Education Program's ATP III definition of the metabolic syndrome and CVD. The metabolic syndrome was present in about 23 percent of individuals without diabetes or prevalent CVD at baseline. Over an average of 11 years of follow-up, 879 incidents of CHD and 219 ischemic stroke events occurred. Men and women with the metabolic syndrome were approximately 1.5 and 2 times more likely to develop CHD than control subjects after adjustment for age, smoking, LDL-C and race. Similar associations were found for stroke.

Clinical trials of the benefits of various therapies that reduce dyslipidemia, in the general population and diabetics

1. Treatment of Glucose Levels

- The **UK Prospective Diabetes Study (UKPDS)** was a 20-year study that recruited 5,102 patients with type 2 diabetes at 23 clinical centers. The study was designed to answer the question, "Can the risk of complications in patients with type 2 diabetes be reduced by intensive blood glucose control?" The study, completed in 1998, showed that risk of macrovascular complications of diabetes, such as myocardial infarction and stroke, were not substantially reduced by intensive blood glucose control. In contrast, the risk of microvascular complication of diabetes, such as retinopathy, was significantly reduced by intensive blood glucose control. Many of these same macrovascular endpoints are impacted by elevated cholesterol lipid abnormalities, including elevated LDL-C and decreased HDL-C. This suggests that effective control of both glucose and lipids can impact cardiovascular diseases.

- The **Epidemiology of Diabetes Interventions and Complications (EDIC)** is a follow-up of the **Diabetes Control and Complications Trial (DCCT)** that was initiated 20 years ago and involved 1,441 people with type 1 diabetes in a comparison of intensive vs conventional blood glucose control. It yielded results similar to the UKPDS. Most participants then enrolled in EDIC, an observational study in which they simply have an annual assessment. Gradually, glucose levels in the intensive control group rose and those in the conventional control group fell. By 1993, they were virtually the same. Yet, compared to the conventional control group, that original tight blood glucose control for an average of six-and-a-half years ultimately yielded reduced coronary calcification, a marker of atherosclerosis in the intensive control group. While the mechanism of such benefits remains unknown, some researchers believe it may be due to a cascade of metabolic effects triggered by high glucose levels. Although the DCCT involved people with type 1 diabetes, it is not unwarranted to believe that some of the same principles apply in type 2.

2. Treatment of Lipid Levels – Statins and/or Niacin

- The **Collaborative Atorvastatin Diabetes Study (CARDS)**, comparing treatment with atorvastatin versus placebo in 2,800 patients with type 2 diabetes but without overt heart disease, was halted two years earlier than planned (in June 2003) because of a significantly lower incidence of fatal and nonfatal coronary events, stroke, and coronary revascularization procedures in treated patients. Co-principal investigator Professor Helen M. Colhoun of the University College and Middlesex School of Medicine, London, reported in June 2003: "If the final data confirm our current findings, as we expect them to, then taken together with the data from HPS (Heart Protection Study) and ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), it would provide a strong evidence base to underpin a change in CVD-prevention guidelines that would affect a large proportion of type 2 diabetic patients." The change? Considering a statin therapy for suitable patients with diabetes in the UK whether or not they have diagnosed heart disease.
- The **Heart Protection Study (HPS)** showed that treatment with simvastatin cut the incidence of heart attack, stroke and revascularization in the diabetic subgroup of about 6,000 patients by about one-quarter, approximately the same benefit as that seen in the overall HPS population. "The present study provides direct evidence that cholesterol-lowering therapy is beneficial for people with diabetes even if they do not already have manifest coronary disease or high cholesterol concentrations," said lead author Dr. Rory Collins of the Clinical Trial Service Unit, Oxford, UK. "Statin therapy should now be considered routinely for all diabetic patients at sufficiently high risk of major vascular events, irrespective of their initial cholesterol concentrations."
- The **Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)** was stopped in 2003 after 3.3 years of a planned five-year follow-up due to a significant reduction in cardiovascular outcomes among hypertensive patients with normal cholesterol levels who were on cholesterol-lowering treatment. Patients in ASCOT with normal or mildly elevated cholesterol who took atorvastatin had 36 percent fewer fatal coronary events and nonfatal MIs than patients treated with placebo.
- The **Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT)** studied the secondary prevention of heart attack or death from coronary causes in men with coronary artery disease and low levels (<40 mg/dL) of HDL cholesterol. It found that a fibrate (gemfibrozil) was associated with a 22 percent reduction in the relative risk of death from CHD or nonfatal myocardial infarction. Gemfibrozil reduced the relative risks of death due to CHD (-22 percent; *P*=0.07), investigator-designated stroke (-29 percent; *P*=0.04), nonfatal MI (-23 percent; *P*=0.02), and death from any cause (-11 percent; *P*=0.23). This study is important because it shows treatment benefits for patients with low HDL-C levels.

- **Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER 2)** was a double-blind, placebo-controlled study of extended-release niacin (1000 mg) on the progression of atherosclerosis in 167 patients with known CHD and moderately low HDL-C, and who were already taking statin therapy. After one year, mean carotid intima-media thickness (CIMT) increased significantly in the placebo group and was unchanged in the niacin group. Clinical CVD events occurred in 3 niacin-treated patients and 7 placebo patients. Thus, the addition of extended-release niacin to background statin therapy slowed progression of atherosclerosis, as evidenced by CIMT.

Who endorses the link between diabetic dyslipidemia, diabetes and heart disease?

The clinical evidence for the link between diabetes, dyslipidemia and heart disease has been reviewed and incorporated into treatment guidelines by the National Cholesterol Education Program's Expert Panel (ATP-III) and the ADA dyslipidemia management guidelines, as well as its standards of care.

- **ATP-III:** Based on an exhaustive survey of clinical data, the most recent guidelines issued by the National Cholesterol Education Program recommend: "Because of growing evidence that many people with diabetes carry a risk for CHD similar to that of people with established CHD, diabetes should be put in a separate category of higher risk."
- **ADA:** The 2005 revised "Standards of Care in Diabetes Mellitus" recognizes that patients with type 2 diabetes have an increased prevalence of lipid abnormalities that contributes to a higher risk of cardiovascular disease. Lipid management aimed at lowering LDL-C, raising HDL-C and lowering triglycerides has been shown to reduce macrovascular disease and mortality in patients with type 2 diabetes, particularly those with poor CV events. Specific lipid goals include:
  - In individuals with diabetes age >40 years with a total cholesterol ≥135 mg/dL, without overt cardiovascular disease, statin therapy to achieve an LDL reduction of 30-40 percent regardless of baseline LDL levels is recommended. The primary goal is an LDL <100 mg/dL (2.6 mmol/L).
  - For persons with diabetes age <40 years without overt cardiovascular disease, but at increased risk (due to other cardiovascular risk factors or long duration of diabetes), who do not achieve lipid goals with lifestyle modifications alone, the addition of pharmacological therapy is appropriate, and the primary goal is an LDL cholesterol <100 mg/dL (2.6 mmol/L).
  - People with diabetes and overt cardiovascular disease are at very high risk for further events and should be treated with a statin. A lower LDL cholesterol goal of <70 mg/dL (1.8 mmol/L), using a high dose of a statin, is an option in these high-risk patients with diabetes and overt cardiovascular disease.

Lifestyle modifications including medical nutrition therapy and physical activity will lead to decreased triglyceride and increased HDL levels and also to modest lowering of LDL cholesterol levels, as well as lower blood glucose levels.

The ADA points out that "Interventions to improve glycemia usually lower triglyceride levels." However, glucose-lowering agents usually do not change or have a modest effect on HDL-C levels, except for thiazolidinediones, which may increase the HDL-C and LDL-C levels, but the long-term effect of such changes is unknown. In general, LDL-C may decrease modestly (up to 10-15 percent) if optimal blood glucose control is achieved.

The ADA advises checking lipid levels regularly, ranging from yearly to every two years, depending on levels at the outset of monitoring.

The Metabolic Syndrome: Putting the Pieces Together

The Metabolic Syndrome: Putting the Pieces Together

7. The Metabolic Syndrome: Putting the Pieces Together

Physicians and scientists generally agree that the metabolic syndrome exists, but there has been disagreement on what to call it. Alternative names include insulin resistance syndrome and Syndrome X.

There is not complete agreement on what factors constitute the metabolic syndrome. For example, according to the American Heart Association, the metabolic syndrome is characterized by a group of risk factors:

- central obesity (excessive fat tissue in and around the abdomen)
- atherogenic dyslipidemia (blood fat disorders – mainly high triglycerides and low HDL-C that foster plaque build-ups in artery walls)
- insulin resistance or glucose intolerance (body can't properly use insulin or blood glucose)
- raised blood pressure (130/85 mm Hg or higher)
- prothrombotic state (e.g., high fibrinogen or plasminogen activator inhibitor in the blood)
- proinflammatory state (e.g., elevated high-sensitivity C-reactive protein in the blood)

The National Cholesterol Education Program definition is similar, but shorter and more specific. It requires three of the following:

- abdominal obesity – waist circumference >40" in men, >35" in women
- triglycerides ≥150 mg/dL
- HDL cholesterol <40 mg/dL in men, <50 mg/dL in women
- hypertension ≥130/85 mm Hg
- fasting glucose ≥110 mg/dL.

Metabolic syndrome has become shorthand for referring to the complexity of risk factors that include "apple-shaped" abdominal obesity, hypertension, insulin resistance and the type of dyslipidemia we have been discussing – elevated or normal LDL-C and triglyceride levels, and reduced HDL-C levels.

Here's one way of looking at it:

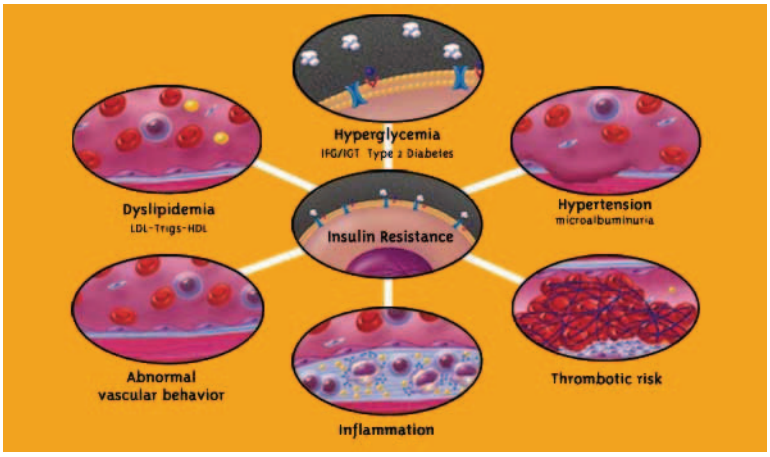


Figure 4. Insulin Resistance and the Metabolic Syndrome

Adapted from: "The Path of Insulin Resistance" Media Briefing by D. Kendall and B. Sobell. June 2003.

Based on the chart above, it is clear that insulin resistance is a common disorder, linking these diverse risk factors and conditions of the metabolic syndrome. An easy way to define the syndrome is **a cluster of metabolic abnormalities that collectively increase the risk of cardiovascular disease and/or type 2 diabetes.**

The components of the metabolic syndrome are unfortunately highly prevalent in the United States, according to the third National Health and Nutrition Examination Survey (NHANES III) from 1988-1994.

It involved questionnaires, physical examinations, and blood tests for 17,030 American adults aged 20 years and older, including a subgroup of 8,476 who had fasting blood tests; after various exclusions, the group was reduced to 6,768, on which these data are based. An estimated 36.3 million (23.4 percent) of the U.S. adult population is estimated to have the metabolic syndrome, and it is about evenly distributed between men and women. Of these, 84 percent met the criteria for obesity, 76 percent for blood pressure, 75 percent for HDL-C, 74 percent for triglycerides, and 41 percent for glucose. Despite the fact that 54 percent are in the higher-risk lipid categories, drug therapy is recommended for only 39 percent.

Figure 5. Characteristics of individuals with the metabolic syndrome in National Health and Nutrition Survey III.

Characteristics	Millions (% of individuals with the metabolic syndrome)
Sex	
Male	16.8 (46.3)
Female	19.5 (53.7)
Diagnostic criteria	
Abdominal obesity	30.3 (83.5)
Male	12.7 (75.6*)
Female	17.6 (90.4*)
Blood Pressure	27.6 (76.1)
High-density lipoprotein cholesterol	27.4 (75.5)
Men	12.3 (73.2*)
Women	15.1 (77.6*)
Triglyceride	26.9 (74.3)
Glucose	14.8 (40.8)
110-125 mg/dL	7.4 (20.3)
≥ 126 mg/dL or diabetics†	7.5 (20.6)

*Percent within each sex.
†As diagnosed by a doctor or requiring insulin or oral diabetics medication.

Figure 5 – Characteristics of Individuals With the Metabolic Syndrome in National Health & Nutrition Examination Survey III

Look at how these factors intertwine: It's been shown that insulin-resistant *pre*-diabetic subjects have more atherogenic risk factors (including higher body mass index, waist circumference, triglyceride concentration and lower HDL-C) than insulin-sensitive pre-diabetic subjects. "People with pre-diabetes are already at increased risk for heart disease and stroke," according to the ADA.

Complications develop slowly – over the course of 20 to 40 years – as can be seen in figure 6 below. This figure shows that the metabolic syndrome (with insulin resistance, dyslipidemia, and hypertension) may exist for 20 years before type 2 diabetes is diagnosed. Macrovascular (big vessel) disease can cause atherosclerosis, coronary heart disease and strokes, and damage to the heart and circulatory system may also occur before type 2 diabetes is diagnosed. Microvascular (small vessel) disease, including diabetic retinopathy (eyes), nephropathy (kidneys) and neuropathy (nerves), is considered a long-term complication of type 2 diabetes.

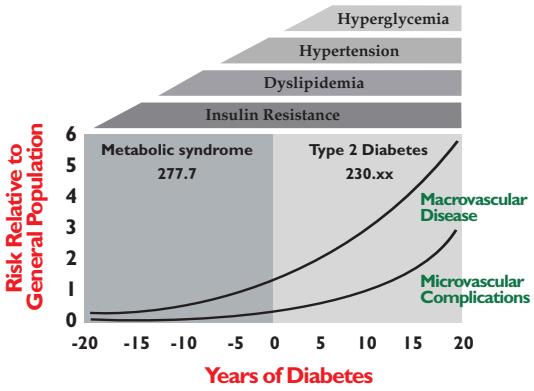


Figure 6. Timeline of the Complications Related to Diabetes and the Metabolic Syndrome

Can it be treated?

The metabolic syndrome has been introduced into the National Cholesterol Education Program ATP III guidelines "in an effort to achieve CVD risk reduction beyond LDL-C lowering therapy. Other clinical guidelines likewise have emphasized the need for more clinical attention to the metabolic syndrome." If intervention can be accomplished with, for example, a medication that addresses several risk factors, that should have positive implications for the patient. For example, thiazolidinediones (TZDs), while primarily affecting blood glucose levels through reduction of insulin resistance, may also improve dyslipidemia. While the effects of TZDs beyond glycemic control relating to the possible prevention or delay of cardiovascular complications of type 2 diabetes have not been determined, the ability of TZDs to affect multiple parameters associated with cardiovascular risk is being investigated in patients at highest risk for CVD.

Integrated Drug Therapy

Integrated Drug Therapy

8. Integrated Drug Therapy

Currently, there is no single treatment that can address all the components of diabetic dyslipidemia. Therefore, a combination of therapies that focuses on the individual components of lipid imbalances is often recommended.

Because of the increased risk of CVD in patients with type 2 diabetes, professional societies including the American Diabetes Association and the National Cholesterol Education Program have issued guidelines for prioritizing treating dyslipidemia in diabetes. As discussed earlier, the first priority is given to lowering LDL-C levels to below 100 mg/dL, followed by strategies to reduce triglyceride and non–HDL-C levels and to raise HDL-C levels.

However, why treat each abnormality one at a time? Researchers are looking for treatments that could address several of the abnormalities inherent in diabetes and diabetic dyslipidemia. At this time, however, such options aren't available.

What oral drugs are used to treat diabetes?

Current oral drugs for diabetes:

- **Sulfonylureas** stimulate the release of insulin and have been available since the 1950s. Chlorpropamide is the only first-generation sulfonylurea that is still around. The second-generation drugs include glyburide and glipizide.
- **Meglinitides** work similarly to sulfonylureas and include repaglinide and nateglinide.
- **Biguanides**, such as metformin, lower blood glucose levels by decreasing the amount of glucose produced by the liver.
- **Thiazolidinediones**, such as pioglitazone or rosiglitazone, help insulin work more efficiently in the body and also reduce glucose production by the liver.
- **Alpha-glucosidase inhibitors**, such as acarbose and meglitol, block the breakdown of starches.

When diet and exercise are not enough to lower blood glucose levels, physicians may prescribe medication. When a single pill does not have the desired effect, combining medications may improve blood glucose control, and this technique is usually more effective than switching from one single medication to another. "When monotherapy fails, a second drug with a different mechanism of action should be added. When two drugs fail, a third oral agent or insulin should be added. Insulin should not be postponed when oral therapy fails to control blood glucose."

What oral drugs are used to treat diabetic dyslipidemia?

The goal of therapy for diabetic dyslipidemia is to have all lipoproteins in the desirable range. This will usually entail utilizing a combination of medications:

- **LDL-C Lowering:** Statins, also known as the HMG CoA reductase inhibitors, are usually the first choice. Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin are the most often prescribed LDL-C lowering drugs. Bile acid sequestrants, such as colesevelam, cholestyramine and colestipol, are alternative choices for LDL-C lowering medications.
- **HDL-C Raising:** Lifestyle modifications may be useful to increase HDL-C levels. In addition, nicotinic acid, that is, niacin, or fibrates (such as gemfibrozil or fenofibrate) can be used.
- **Triglyceride Lowering:** Blood glucose control is the first priority in lowering triglycerides in diabetes; however, fibrates can be effective as well. Lastly, high doses of statins are moderately effective in patients who also have high LDL-C.
- **Combined Hyperlipidemia:** Improved glycemic control combined with a statin is the first treatment choice for this condition. Adding or replacing with a fibrate or niacin can provide an additive effect.

Do any medications hold potential as integrated drug therapies?

First, let's consider traditional lipid-lowering drugs and their benefits in diabetic dyslipidemia. Do any of them offer benefits beyond LDL-C lowering – any impact on the classic lipid disorder seen in diabetic dyslipidemia?

- **Statins** have been shown to reduce LDL-C and triglycerides and moderately increase HDL-C.
- **Fibric acid derivatives** reduce triglycerides and modestly increase HDL-C.
- **Cholesterol absorption inhibitors** reduce LDL-C slightly, decrease triglycerides, and slightly increase HDL.

Second, let's consider traditional anti-diabetes therapies. Do any of them also have benefits against dyslipidemia?

- **PPARγ agonists** (pronounce it *pee-par gamma*)
  Also known as thiazolidinediones (*thigh-uh-ZAHL-uh-deen-DIE-ownz*) or glitazones, PPARγ agonists lower glucose levels by reducing insulin resistance in patients with type 2 diabetes. But pioglitazone, a drug in this class, has been shown to have an additional benefit beyond lowering blood glucose levels. In clinical trials, pioglitazone has been shown to improve HDL-C, triglycerides, and LDL-C particle size with no change in LDL-C levels. In addition, it's been shown to reduce the atherogenic dense LDL-C particles.

  All PPARγ agonists may not be alike in their effect on dyslipidemia. In a randomized, double-blind, multicenter 24-week trial comparing the impact of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia, both drugs had similar effects on lowering blood glucose levels. However, pioglitazone was associated with significant reductions in triglycerides, and greater increases in HDL-C, compared to rosiglitazone. In this study, pioglitazone therapy resulted in a more favorable lipid profile than rosiglitazone therapy.

New study: To determine whether treatment with pioglitazone can prevent secondary macrovascular events in diabetes, an ongoing clinical trial in Europe called PROactive (**PRO**spective Pioglit**A**zone **C**linical **T**rial **I**n Macro**V**ascular **E**vents) is being conducted. The study has enrolled 5,238 patients in 19 countries who have experienced one or more macrovascular events such as a heart attack, coronary artery bypass surgery, or stroke. Patients have been randomized to receive pioglitazone or placebo in addition to their existing therapy. They will be followed until the occurrence of a new macrovascular event or death, and follow-up is estimated at four years.

Important Product Information

- ***ACTOS® (pioglitazone HCl)***

  ACTOS is not for everyone. ACTOS can cause fluid retention that may lead to or worsen heart failure, so tell your doctor if you have a history of these conditions. Talk to your doctor immediately if you experience rapid weight gain, fluid retention, or shortness of breath while taking ACTOS. If you have moderate to severe heart failure, ACTOS is not recommended. Your doctor should perform a blood test to check for liver problems before you start ACTOS and periodically thereafter. Do not take ACTOS if you have active liver disease. Talk to your doctor immediately if you experience nausea, vomiting, stomach pain, tiredness, loss of appetite, dark urine, or yellowing of the skin.

  If you are of childbearing age, talk to your doctor before taking ACTOS as it could increase your chance of becoming pregnant.

  Some people taking ACTOS may experience flu-like symptoms, mild to moderate swelling of legs and ankles, and anemia. When taking ACTOS with insulin or sulfonylureas, you may be at risk for low blood glucose.

  Management of type 2 diabetes requires nutritional counseling, weight reduction as needed, and exercise. When diet and exercise are not enough, ACTOS may be used alone or in combination with sulfonylureas, metformin or insulin to improve blood glucose control. ACTOS should not be used in the treatment of type 1 diabetes.

  Please see accompanying complete prescribing information for ACTOS at the end of this booklet.

- **Acarbose**

  Acarbose is an oral medicine to treat type 2 diabetes. It blocks the enzymes that digest starches in food, which results in a slower and lower rise in blood glucose throughout the day. It has been shown to delay the development of type 2 diabetes in pre-diabetics with impaired glucose tolerance. Further, acarbose also has been shown to increase HDL and decrease LDL, making it an interesting candidate for integrated therapy. However, many patients stop taking acarbose because it can be associated with uncomfortable side effects such as diarrhea and flatulence due to osmotic effects and bacterial fermentation. Beginning with low doses and increasing slowly can minimize these effects.

- **Metformin**

  A biguanide, metformin is another oral agent that successfully lowers glucose levels. It primarily decreases the liver's output of glucose and, to a lesser extent, increases utilization of glucose. It, too, has been found effective in delaying the development of type 2 diabetes in pre-diabetics with impaired glucose tolerance. According to a recent systematic review, metformin (at higher doses) reduces total cholesterol but had no effect on triglycerides. Metformin can cause nausea, diarrhea, and abdominal pain, which can be minimized by increasing the dose slowly and taking the drug with food. While lactic acidosis is a rare but potentially fatal complication, it can usually be prevented by avoiding metformin use in those with impaired kidney function, congestive heart failure, liver failure, alcohol abuse, and during pregnancy and during or shortly after major surgery and radiographic studies involving injected iodine.

The Future

9. The Future

What is the prognosis for treating patients who have diabetic dyslipidemia?

Aggressive control of risk factors is crucial to improve health outcomes for people with diabetes. In particular, keeping blood glucose, cholesterol and other lipids under control can help to prevent diabetes complications – including heart attack and stroke.

Unfortunately, the current state of control of blood glucose, blood pressure, and cholesterol among patients with diabetes in the United States is inadequate:

- Only 7.3 percent of individuals with diabetes achieve the national goals for A1C, blood pressure, and cholesterol levels.
- The proportion of adults in the United States with adequately controlled type 2 diabetes decreased in the past decade. A partial explanation for this could be that patients tend to be younger, weigh more and have a longer duration of diabetes.

Recent Studies Underscore the Need for More Adequate Control in the Future

A 2004 chart review study showed, for example, that among patients with type 2 diabetes, the majority failed to attain lipid goals set by the American Diabetes Association. For HDL-C, the target goal was achieved by 42 percent of the patients. For LDL-C, the goal was reached by 47 percent and the triglyceride goal was reached by 70 percent of the patients. All three lipid goals, however, were achieved by only 14.6 percent of the study population.

A retrospective study reported at the 2004 American Diabetes Association Scientific Sessions showed that lipid testing, treatment, goal attainment rates, and lipid levels in diabetes patients have generally improved. However, another similarly designed study found that combined LDL-C, HDL-C and triglyceride goal attainment is sub-optimal at about 17 percent.

A worldwide survey of physician attitudes demonstrated a disparity in the management of dyslipidemia in patients with type 2 diabetes and cardiovascular disease versus those without cardiovascular disease. A higher percentage of physicians aim to achieve a lower LDL-C treatment goal in diabetes patients with cardiovascular disease versus those without.

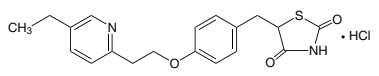
Bottom line, further public health efforts are needed to control risk factors for CVD among individuals with diabetes.

ACTOS®
(pioglitazone hydrochloride) Tablets

DESCRIPTION

ACTOS (pioglitazone hydrochloride) is an oral antidiabetic agent that acts primarily by decreasing insulin resistance. ACTOS is used in the management of type 2 diabetes mellitus (also known as non-insulin-dependent diabetes mellitus [NIDDM] or adult-onset diabetes). Pharmacological studies indicate that ACTOS improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. ACTOS improves glycemic control while reducing circulating insulin levels.

Pioglitazone [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-] thiazolidinedione monohydrochloride belongs to a different chemical class and has a different pharmacological action than the sulfonylureas, metformin, or the α-glucosidase inhibitors. The molecule contains one asymmetric carbon, and the compound is synthesized and used as the racemic mixture. The two enantiomers of pioglitazone interconvert in vivo. No differences were found in the pharmacologic activity between the two enantiomers. The structural formula is as shown:



Pioglitazone hydrochloride is an odorless white crystalline powder that has a molecular formula of $C_{19}H_{20}N_2O_3S$•HCl and a molecular weight of 392.90 daltons. It is soluble in N,N-dimethylformamide, slightly soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water, and insoluble in ether.

ACTOS is available as a tablet for oral administration containing 15 mg, 30 mg, or 45 mg of pioglitazone (as the base) formulated with the following excipients: lactose monohydrate NF, hydroxypropylcellulose NF, carboxymethylcellulose calcium NF, and magnesium stearate NF.

CLINICAL PHARMACOLOGY

Mechanism of Action

ACTOS is a thiazolidinedione antidiabetic agent that depends on the presence of insulin for its mechanism of action. ACTOS decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Unlike sulfonylureas, pioglitazone is not an insulin secretagogue. Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.

In animal models of diabetes, pioglitazone reduces the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia characteristic of insulin-resistant states such as type 2 diabetes. The metabolic changes produced by pioglitazone result in increased responsiveness of insulin-dependent tissues and are observed in numerous animal models of insulin resistance.

Since pioglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in animal models that lack endogenous insulin.

Pharmacokinetics and Drug Metabolism

Serum concentrations of total pioglitazone (pioglitazone plus active metabolites) remain elevated 24 hours after once daily dosing. Steady-state serum concentrations of both pioglitazone and total pioglitazone are achieved within 7 days. At steady-state, two of the pharmacologically active metabolites of pioglitazone, Metabolites III (M-III) and IV (M-IV), reach serum concentrations equal to or greater than pioglitazone. In both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the peak total pioglitazone serum concentrations and 20% to 25% of the total area under the serum concentration-time curve (AUC).

Maximum serum concentration (C_{max}), AUC, and trough serum concentrations (C_{min}) for both pioglitazone and total pioglitazone increase proportionally at doses of 15 mg and 30 mg per day. There is a slightly less than proportional increase for pioglitazone and total pioglitazone at a dose of 60 mg per day.

Absorption: Following oral administration, in the fasting state, pioglitazone is first measurable in serum within 30 minutes, with peak concentrations observed within 2 hours. Food slightly delays the time to peak serum concentration to 3 to 4 hours, but does not alter the extent of absorption.

Distribution: The mean apparent volume of distribution (Vd/F) of pioglitazone following single-dose administration is 0.63 ± 0.41 (mean ± SD) L/kg of body weight. Pioglitazone is extensively protein bound (>99%) in human serum, principally to serum albumin. Pioglitazone also binds to other serum proteins, but with lower affinity. Metabolites M-III and M-IV also are extensively bound (> 98%) to serum albumin.

Metabolism: Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-II and M-IV (hydroxy derivatives of pioglitazone) and M-III (keto derivative of pioglitazone) are pharmacologically active in animal models of type 2 diabetes. In addition to pioglitazone, M-III and M-IV are the principal drug-related species found in human serum following multiple dosing. At steady-state, in both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the total peak serum concentrations and 20% to 25% of the total AUC.

In vitro data demonstrate that multiple CYP isoforms are involved in the metabolism of pioglitazone. The cytochrome P450 isoforms involved are CYP2C8 and, to a lesser degree, CYP3A4 with additional contributions from a variety of other isoforms including the mainly extrahepatic CYP1A1. In vivo studies of pioglitazone in combination with P450 inhibitors and substrates have been performed (see Drug Interactions). Urinary 6β-hydroxycortisol/cortisol ratios measured in patients treated with ACTOS showed that pioglitazone is not a strong CYP3A4 enzyme inducer.

Excretion and Elimination: Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces.

The mean serum half-life of pioglitazone and total pioglitazone ranges from 3 to 7 hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be 5 to 7 L/hr.

Special Populations

Renal Insufficiency: The serum elimination half-life of pioglitazone, M-III, and M-IV remains unchanged in patients with moderate (creatinine clearance 30 to 60 mL/min) to severe (creatinine clearance <30 mL/min) renal impairment when compared to normal subjects. No dose adjustment in patients with renal dysfunction is recommended (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: Compared with normal controls, subjects with impaired hepatic function (Child-Pugh Grade B/C) have an approximate 45% reduction in pioglitazone and total pioglitazone mean peak concentrations but no change in the mean AUC values.

ACTOS therapy should not be initiated if the patient exhibits clinical evidence of active liver disease or serum transaminase levels (ALT) exceed 2.5 times the upper limit of normal (see PRECAUTIONS, Hepatic Effects).

Elderly: In healthy elderly subjects, peak serum concentrations of pioglitazone and total pioglitazone are not significantly different, but AUC values are slightly higher and the terminal half-life values slightly longer than for younger subjects. These changes were not of a magnitude that would be considered clinically relevant.

Pediatrics: Pharmacokinetic data in the pediatric population are not available.

Gender: The mean C_{max} and AUC values were increased 20% to 60% in females. As monotherapy and in combination with sulfonylurea, metformin, or insulin, ACTOS improved glycemic control in both males and females. In controlled clinical trials, hemoglobin A_{1c} (HbA_{1c}) decreases from baseline were generally greater for females than for males (average mean difference in HbA_{1c} 0.5%). Since therapy should be individualized for each patient to achieve glycemic control, no dose adjustment is recommended based on gender alone.

Ethnicity: Pharmacokinetic data among various ethnic groups are not available.

Drug-Drug Interactions

The following drugs were studied in healthy volunteers with a co-administration of ACTOS 45 mg once daily. Listed below are the results:

Oral Contraceptives: Co-administration of ACTOS (45 mg once daily) and an oral contraceptive (1 mg norethindrone plus 0.035 mg ethinyl estradiol once daily) for 21 days, resulted in 11% and 11-14% decrease in ethinyl estradiol AUC (0-24h) and C_{max} respectively. There were no significant changes in norethindrone AUC (0-24h) and C_{max}. In view of the high variability of ethinyl estradiol pharmacokinetics, the clinical significance of this finding is unknown.

Fexofenadine HCl: Co-administration of ACTOS for 7 days with 60 mg fexofenadine administered orally twice daily resulted in no significant effect on pioglitazone pharmacokinetics. ACTOS had no significant effect on fexofenadine pharmacokinetics.

Glipizide: Co-administration of ACTOS and 5 mg glipizide administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of glipizide.

Digoxin: Co-administration of ACTOS with 0.25 mg digoxin administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of digoxin.

Warfarin: Co-administration of ACTOS for 7 days with warfarin did not alter the steady-state pharmacokinetics of warfarin. ACTOS has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Metformin: Co-administration of a single dose of metformin (1000 mg) and ACTOS after 7 days of ACTOS did not alter the pharmacokinetics of the single dose of metformin.

Midazolam: Administration of ACTOS for 15 days followed by a single 7.5 mg dose of midazolam syrup resulted in a 26% reduction in midazolam C_{max} and AUC.

Ranitidine HCl: Co-administration of ACTOS for 7 days with ranitidine administered orally twice daily for either 4 or 7 days resulted in no significant effect on pioglitazone pharmacokinetics. ACTOS showed no significant effect on ranitidine pharmacokinetics.

Nifedipine ER: Co-administration of ACTOS for 7 days with 30 mg nifedipine ER administered orally once daily for 4 days to male and female volunteers resulted in least square mean (90% CI) values for unchanged nifedipine of 0.83 (0.73-0.95) for C_{max} and 0.88 (0.80-0.96) for AUC. In view of the high variability of nifedipine pharmacokinetics, the clinical significance of this finding is unknown.

Ketoconazole: Co-administration of ACTOS for 7 days with ketoconazole 200 mg administered twice daily resulted in least square mean (90% CI) values for unchanged pioglitazone of 1.14 (1.06 - 1.23) for C_{max}, 1.34 (1.26 - 1.41) for AUC and 1.87 (1.71 - 2.04) for C_{min}.

Atorvastatin Calcium: Co-administration of ACTOS for 7 days with atorvastatin calcium (LIPITOR®) 80 mg once daily resulted in least square mean (90% CI) values for unchanged pioglitazone of 0.69 (0.57 - 0.85) for C_{max}, 0.76 (0.65 - 0.88) for AUC and 0.96 (0.87 - 1.05) for C_{min}. For unchanged atorvastatin the least square mean (90% CI) values were 0.77 (0.66 - 0.90) for C_{max}, 0.86 (0.78 - 0.94) for AUC and 0.92 (0.82 - 1.02) for C_{min}.

Theophylline: Co-administration of ACTOS for 7 days with theophylline 400 mg administered twice daily resulted in no change in the pharmacokinetics of either drug.

Cytochrome P450: See **PRECAUTIONS**.

Pharmacodynamics and Clinical Effects

Clinical studies demonstrate that ACTOS improves insulin sensitivity in insulin-resistant patients. ACTOS enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal, improves hepatic sensitivity to insulin, and improves dysfunctional glucose homeostasis. In patients with type 2 diabetes, the decreased insulin resistance produced by ACTOS results in lower plasma glucose concentrations, lower plasma insulin levels, and lower HbA_{1c} values. Based on results from an open-label extension study, the glucose lowering effects of ACTOS appear to persist for at least one year. In controlled clinical trials, ACTOS in combination with sulfonylurea, metformin, or insulin had an additive effect on glycemic control.

Patients with lipid abnormalities were included in clinical trials with ACTOS. Overall, patients treated with ACTOS had mean decreases in triglycerides, mean increases in HDL cholesterol, and no consistent mean changes in LDL and total cholesterol.

In a 26-week, placebo-controlled, dose-ranging study, mean triglyceride levels decreased in the 15 mg, 30 mg, and 45 mg ACTOS dose groups compared to a mean increase in the placebo group. Mean HDL levels increased to a greater extent in patients treated with ACTOS than in the placebo-treated patients. There were no consistent differences for LDL and total cholesterol in patients treated with ACTOS compared to placebo (Table 1).

Table 1 Lipids in a 26-Week Placebo-Controlled Monotherapy Dose-Ranging Study

	Placebo	ACTOS 15 mg Once Daily	ACTOS 30 mg Once Daily	ACTOS 45 mg Once Daily
Triglycerides (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	262.8	283.8	261.1	259.7
Percent change from baseline (mean)	4.8%	-9.0%	-9.6%	-9.3%
HDL Cholesterol (mg/dL)	N=79	N=79	N=83	N=77
Baseline (mean)	41.7	40.4	40.8	40.7
Percent change from baseline (mean)	8.1%	14.1%	12.2%	19.1%
LDL Cholesterol (mg/dL)	N=65	N=63	N=74	N=62
Baseline (mean)	138.8	131.9	135.6	126.8
Percent change from baseline (mean)	4.8%	7.2%	5.2%	6.0%
Total Cholesterol (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	224.6	220.0	222.7	213.7
Percent change from baseline (mean)	4.4%	4.6%	3.3%	6.4%

In the two other monotherapy studies (24 weeks and 16 weeks) and in combination therapy studies with sulfonylurea (24 weeks and 16 weeks) and metformin (24 weeks and 16 weeks), the results were generally consistent with the data above. In placebo-controlled trials, the placebo-corrected mean changes from baseline decreased 5% to 26% for triglycerides and increased 6% to 13% for HDL in patients treated with ACTOS. A similar pattern of results was seen in 24-week combination therapy studies of ACTOS with sulfonylurea or metformin.

In a combination therapy study with insulin (16 weeks), the placebo-corrected mean percent change from baseline in triglyceride values for patients treated with ACTOS was also decreased. A placebo-corrected mean change from baseline in LDL cholesterol of 7% was observed for the 15 mg dose group. Similar results to those noted above for HDL and total cholesterol were observed. A similar pattern of results was seen in a 24-week combination therapy study with ACTOS with insulin.

Clinical Studies

Monotherapy

In the U.S., three randomized, double-blind, placebo-controlled trials with durations from 16 to 26 weeks were conducted to evaluate the use of ACTOS as monotherapy in patients with type 2 diabetes. These studies examined ACTOS at doses up to 45 mg or placebo once daily in 865 patients.

In a 26-week dose-ranging study, 408 patients with type 2 diabetes were randomized to receive 7.5 mg, 15 mg, 30 mg, or 45 mg of ACTOS, or placebo once daily. Therapy with any previous antidiabetic agent was discontinued 8 weeks prior to the double-blind period. Treatment with 15 mg, 30 mg, and 45 mg of ACTOS produced statistically significant improvements in HbA_{1c} and fasting plasma glucose (FPG) at endpoint compared to placebo (see Figure 1, Table 2).

Figure 1 shows the time course for changes in FPG and HbA_{1c} for the entire study population in this 26-week study.

Figure 1 Mean Change from Baseline for FPG and HbA_{1c} in a 26-Week Placebo-Controlled Dose-Ranging Study

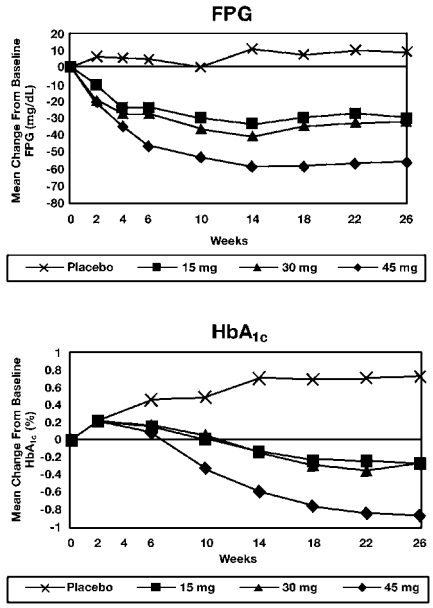


Table 2 shows HbA_{1c} and FPG values for the entire study population.

Table 2 Glycemic Parameters in a 26-Week Placebo-Controlled Dose-Ranging Study

	Placebo	ACTOS 15 mg Once Daily	ACTOS 30 mg Once Daily	ACTOS 45 mg Once Daily
Total Population				
HbA_{1c} (%)	N=79	N=79	N=85	N=76
Baseline (mean)	10.4	10.2	10.2	10.3
Change from baseline (adjusted mean†)	0.7	-0.3	-0.3	-0.9
Difference from placebo (adjusted mean†)		-1.0*	-1.0*	-1.6*
FPG (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	268	267	269	276
Change from baseline (adjusted mean†)	9	-30	-32	-56
Difference from placebo (adjusted mean†)		-39*	-41*	-65*

†Adjusted for baseline, pooled center, and pooled center by treatment interaction
*p ≤ 0.050 vs. placebo

The study population included patients not previously treated with antidiabetic medication (naïve; 31%) and patients who were receiving antidiabetic medication at the time of study enrollment (previously treated; 69%). The data for the naïve and previously-treated patient subsets are shown in Table 3. All patients entered an 8 week washout/run-in period prior to double-blind treatment. This run-in period was associated with little change in HbA_{1c} and FPG values from screening to baseline for the naïve patients; however, for the previously-treated group, washout from previous antidiabetic medication resulted in deterioration of glycemic control and increases in HbA_{1c} and FPG. Although most patients in the previously-treated group had a decrease from baseline in HbA_{1c} and FPG with ACTOS, in many cases the values did not return to screening levels by the end of the study. The study design did not permit the evaluation of patients who switched directly to ACTOS from another antidiabetic agent.

Table 3 Glycemic Parameters in a 26-Week Placebo-Controlled Dose-Ranging Study

	Placebo	ACTOS 15 mg Once Daily	ACTOS 30 mg Once Daily	ACTOS 45 mg Once Daily
Naïve to Therapy				
HbA_{1c} (%)	N=25	N=26	N=26	N=21
Screening (mean)	9.3	10.0	9.5	9.8
Baseline (mean)	9.0	9.9	9.3	10.0
Change from baseline (adjusted mean*)	0.6	-0.8	-0.6	-1.9
Difference from placebo (adjusted mean*)		-1.4	-1.3	-2.6
FPG (mg/dL)	N=25	N=26	N=26	N=21
Screening (mean)	223	245	239	239
Baseline (mean)	229	251	225	235
Change from baseline (adjusted mean*)	16	-37	-41	-64
Difference from placebo (adjusted mean*)		-52	-56	-80
Previously Treated				
HbA_{1c} (%)	N=54	N=53	N=59	N=55
Screening (mean)	9.3	9.0	9.1	9.0
Baseline (mean)	10.9	10.4	10.4	10.6
Change from baseline (adjusted mean*)	0.8	-0.1	-0.0	-0.6
Difference from placebo (adjusted mean*)		-1.0	-0.9	-1.4
FPG (mg/dL)	N=54	N=53	N=58	N=56
Screening (mean)	222	209	230	215
Baseline (mean)	285	275	286	292
Change from baseline (adjusted mean*)	4	-32	-27	-55
Difference from placebo (adjusted mean*)		-36	-31	-59

* Adjusted for baseline and pooled center

In a 24-week placebo-controlled study, 260 patients with type 2 diabetes were randomized to one of two forced-titration ACTOS treatment groups or a mock titration placebo group. Therapy with any previous antidiabetic agent was discontinued 6 weeks prior to the double-blind period. In one ACTOS treatment group, patients received an initial dose of 7.5 mg once daily. After four weeks, the dose was increased to 15 mg once daily and after another four weeks, the dose was increased to 30 mg once daily for the remainder of the study (16 weeks). In the second ACTOS treatment group, patients received an initial dose of 15 mg once daily and were titrated to 30 mg once daily and 45 mg once daily in a similar manner. Treatment with ACTOS, as described, produced statistically significant improvements in HbA_{1c} and FPG at endpoint compared to placebo (see Table 4).

Table 4 Glycemic Parameters in a 24-Week Placebo-Controlled Forced-Titration Study

	Placebo	ACTOS 30 mg+ Once Daily	ACTOS 45 mg+ Once Daily
Total Population			
HbA_{1c} (%)	N=83	N=85	N=85
Baseline (mean)	10.8	10.3	10.8
Change from baseline (adjusted mean++)	0.9	-0.6	-0.6
Difference from placebo (adjusted mean++)		-1.5*	-1.5*
FPG (mg/dL)	N=78	N=82	N=85
Baseline (mean)	279	268	281
Change from baseline (adjusted mean++)	18	-44	-50
Difference from placebo (adjusted mean++)		-62*	-68*

+Final dose in forced titration
++ Adjusted for baseline, pooled center, and pooled center by treatment interaction
* $p \leq 0.050$ vs. placebo

For patients who had not been previously treated with antidiabetic medication (24%), mean values at screening were 10.1% for HbA_{1c} and 238 mg/dL for FPG. At baseline, mean HbA_{1c} was 10.2% and mean FPG was 243 mg/dL. Compared with placebo, treatment with ACTOS titrated to a final dose of 30 mg and 45 mg resulted in reductions from baseline in mean HbA_{1c} of 2.3% and 2.6% and mean FPG of 63 mg/dL and 95 mg/dL, respectively. For patients who had been previously treated with antidiabetic medication (76%), this medication was discontinued at screening. Mean values at screening were 9.4% for HbA_{1c} and 216 mg/dL for FPG. At baseline, mean HbA_{1c} was 10.7% and mean FPG was 290 mg/dL. Compared with placebo, treatment with ACTOS titrated to a final dose of 30 mg and 45 mg resulted in reductions from baseline in mean HbA_{1c} of 1.3% and 1.4% and mean FPG of 55 mg/dL and 60 mg/dL, respectively. For many previously-treated patients, HbA_{1c} and FPG had not returned to screening levels by the end of the study.

In a 16-week study, 197 patients with type 2 diabetes were randomized to treatment with 30 mg of ACTOS or placebo once daily. Therapy with any previous antidiabetic agent was discontinued 6 weeks prior to the double-blind period. Treatment with 30 mg of ACTOS produced statistically significant improvements in HbA_{1c} and FPG at endpoint compared to placebo (see Table 5).

Table 5 Glycemic Parameters in a 16-Week Placebo-Controlled Study

	Placebo	ACTOS 30 mg Once Daily
Total Population		
HbA_{1c} (%)	N=93	N=100
Baseline (mean)	10.3	10.5
Change from baseline (adjusted mean+)	0.8	-0.6
Difference from placebo (adjusted mean+)		-1.4*
FPG (mg/dL)	N=91	N=99
Baseline (mean)	270	273
Change from baseline (adjusted mean+)	8	-50
Difference from placebo (adjusted mean+)		-58*

+ Adjusted for baseline, pooled center, and pooled center by treatment interaction
* $p \leq 0.050$ vs. placebo

For patients who had not been previously treated with antidiabetic medication (40%), mean values at screening were 10.3% for HbA_{1c} and 240 mg/dL for FPG. At baseline, mean HbA_{1c} was 10.4% and mean FPG was 254 mg/dL. Compared with placebo, treatment with ACTOS 30 mg resulted in reductions from baseline in mean HbA_{1c} of 1.0% and mean FPG of 62 mg/dL. For patients who had been previously treated with antidiabetic medication (60%), this medication was discontinued at screening. Mean values at screening were 9.4% for HbA_{1c} and 216 mg/dL for FPG. At baseline, mean HbA_{1c} was 10.6% and mean FPG was 287 mg/dL. Compared with placebo, treatment with ACTOS 30 mg resulted in reductions from baseline in mean HbA_{1c} of 1.3% and mean FPG of 46 mg/dL. For many previously-treated patients, HbA_{1c} and FPG had not returned to screening levels by the end of the study.

Combination Therapy
Three 16-week, randomized, double-blind, placebo-controlled clinical studies and three 24-week randomized, double-blind, dose-controlled clinical studies were conducted to evaluate the effects of ACTOS on glycemic control in patients with type 2 diabetes who were inadequately controlled ($HbA_{1c} \geq 8\%$) despite current therapy with a sulfonylurea, metformin, or insulin. Previous diabetes treatment may have been monotherapy or combination therapy.

ACTOS Plus Sulfonylurea Studies
Two clinical studies were conducted with ACTOS in combination with a sulfonylurea. Both studies included patients with type 2 diabetes on a sulfonylurea, either alone or in combination with another antidiabetic agent. All other antidiabetic agents were withdrawn prior to starting study treatment. In the first study, 560 patients were randomized to receive 15 mg or 30 mg of ACTOS or placebo once daily for 16 weeks in addition to their current sulfonylurea regimen. When compared to placebo at Week 16, the addition of ACTOS to the sulfonylurea significantly reduced the mean HbA_{1c} by 0.9% and 1.3% and mean FPG by 39 mg/dL and 58 mg/dL for the 15 mg and 30 mg doses, respectively.

In the second study, 702 patients were randomized to receive 30 mg or 45 mg of ACTOS once daily for 24 weeks in addition to their current sulfonylurea regimen. The mean reductions from baseline at Week 24 in HbA_{1c} were 1.55% and 1.67% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 51.5 mg/dL and 56.1 mg/dL.

The therapeutic effect of ACTOS in combination with sulfonylurea was observed in patients regardless of whether the patients were receiving low, medium, or high doses of sulfonylurea.

ACTOS Plus Metformin Studies
Two clinical studies were conducted with ACTOS in combination with metformin. Both studies included patients with type 2 diabetes on metformin, either alone or in combination with another antidiabetic agent. All other antidiabetic agents were withdrawn prior to starting study treatment. In the first study, 328 patients were randomized to receive either 30 mg of ACTOS or placebo once daily for 16 weeks in addition to their current metformin regimen. When compared to placebo at Week 16, the addition of ACTOS to metformin significantly reduced the mean HbA_{1c} by 0.8% and decreased the mean FPG by 38 mg/dL.

In the second study, 827 patients were randomized to receive either 30 mg or 45 mg of ACTOS once daily for 24 weeks in addition to their current metformin regimen. The mean reductions from baseline at Week 24 in HbA_{1c} were 0.80% and 1.01% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 38.2 mg/dL and 50.7 mg/dL.

The therapeutic effect of ACTOS in combination with metformin was observed in patients regardless of whether the patients were receiving lower or higher doses of metformin.

ACTOS Plus Insulin Studies
Two clinical studies were conducted with ACTOS in combination with insulin. Both studies included patients with type 2 diabetes on insulin, either alone or in combination with another antidiabetic agent. All other antidiabetic agents were withdrawn prior to starting study treatment. In the first study, 566 patients receiving a median of 60.5 units per day of insulin were randomized to receive either 15 mg or 30 mg of ACTOS or placebo once daily for 16 weeks in addition to their insulin regimen. When compared to placebo at Week 16, the addition of ACTOS to insulin significantly reduced both HbA_{1c} by 0.7% and 1.0% and FPG by 35 mg/dL and 49 mg/dL for the 15 mg and 30 mg dose, respectively.

In the second study, 690 patients receiving a median of 60.0 units per day of insulin received either 30 mg or 45 mg of ACTOS once daily for 24 weeks in addition to their current insulin regimen. The mean reductions from baseline at Week 24 in HbA_{1c} were 1.17% and 1.46% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 31.9 mg/dL and 45.8 mg/dL. Improved glycemic control was accompanied by mean decreases from baseline in insulin dose requirements of 6.0% and 9.4% per day for the 30 mg and 45 mg dose, respectively.

The therapeutic effect of ACTOS in combination with insulin was observed in patients regardless of whether the patients were receiving lower or higher doses of insulin.

INDICATIONS AND USAGE
ACTOS is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes (non-insulin-dependent diabetes mellitus, NIDDM). ACTOS is indicated for monotherapy. ACTOS is also indicated for use in combination with a sulfonylurea, metformin, or insulin when diet and exercise plus the single agent does not result in adequate glycemic control.

Management of type 2 diabetes should also include nutritional counseling, weight reduction as needed, and exercise. These efforts are important not only in the primary treatment of type 2 diabetes, but also to maintain the efficacy of drug therapy.

CONTRAINDICATIONS
ACTOS is contraindicated in patients with known hypersensitivity to this product or any of its components.

WARNINGS
Cardiac Failure and Other Cardiac Effects
ACTOS, like other thiazolidinediones, can cause fluid retention when used alone or in combination with other antidiabetic agents, including insulin. Fluid retention may lead to or exacerbate heart failure. Patients should be observed for signs and symptoms of heart failure (see Information for Patients). ACTOS should be discontinued if any deterioration in cardiac status occurs. Patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied during pre-approval clinical trials; ACTOS is not recommended in these patients (see PRECAUTIONS, Cardiovascular).

In one 16-week U.S. double-blind, placebo-controlled clinical trial involving 566 patients with type 2 diabetes, ACTOS at doses of 15 mg and 30 mg in combination with insulin was compared to insulin therapy alone. This trial included patients with long-standing diabetes and a high prevalence of pre-existing medical conditions as follows: arterial hypertension (57.2%), peripheral neuropathy (22.6%), coronary heart disease (19.6%), retinopathy (13.1%), myocardial infarction (8.8%), vascular disease (6.4%), angina pectoris (4.4%), stroke and/or transient ischemic attack (4.1%), and congestive heart failure (2.3%).

In this study two of the 191 patients receiving 15 mg ACTOS plus insulin (1.1%) and two of the 188 patients receiving 30 mg ACTOS plus insulin (1.1%) developed congestive heart failure compared with none of the 187 patients on insulin therapy alone. All four of these patients had previous histories of cardiovascular conditions including coronary artery disease, previous CABG procedures, and myocardial infarction. In a 24-week dose-controlled study in which ACTOS was coadministered with insulin, 0.3% of patients (1/345) on 30 mg and 0.9% (3/345) of patients on 45 mg reported CHF as a serious adverse event.

Analysis of data from these studies did not identify specific factors that predict increased risk of congestive heart failure on combination therapy with insulin.

In type 2 diabetes and congestive heart failure (systolic dysfunction)

A 24-week post-marketing safety study was performed to compare ACTOS (n=262) to glyburide (n=256) in uncontrolled diabetic patients (mean HbA_{1c} 8.8% at baseline) with NYHA Class II and III heart failure and ejection fraction less than 40% (mean EF 30% at baseline). Over the course of the study, overnight hospitalization for congestive heart failure was reported in 9.9% of patients on ACTOS compared to 4.7% of patients on glyburide with a treatment difference observed from 6 weeks. This adverse event associated with ACTOS was more marked in patients using insulin at baseline and in patients over 64 years of age. No difference in cardiovascular mortality between the treatment groups was observed.

ACTOS should be initiated at the lowest approved dose if it is prescribed for patients with type 2 diabetes and systolic heart failure (NYHA Class II). If subsequent dose escalation is necessary, the dose should be increased gradually only after several months of treatment with careful monitoring for weight gain, edema, or signs and symptoms of CHF exacerbation.

PRECAUTIONS
General
ACTOS exerts its antihyperglycemic effect only in the presence of insulin. Therefore, ACTOS should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Hypoglycemia: Patients receiving ACTOS in combination with insulin or oral hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

Cardiovascular: In U.S. placebo-controlled clinical trials that excluded patients with New York Heart Association (NYHA) Class III and IV cardiac status, the incidence of serious cardiac adverse events related to volume expansion was not increased in patients treated with ACTOS as monotherapy or in combination with sulfonylureas or metformin vs. placebo-treated patients. In insulin combination studies, a small number of patients with a history of previously existing cardiac disease developed congestive heart failure when treated with ACTOS in combination with insulin (see WARNINGS). Patients with NYHA Class III and IV cardiac status were not studied in these ACTOS clinical trials. ACTOS is not indicated in patients with NYHA Class III or IV cardiac status.

In postmarketing experience with ACTOS, cases of congestive heart failure have been reported in patients both with and without previously known heart disease.

Edema: ACTOS should be used with caution in patients with edema. In all U.S. clinical trials, edema was reported more frequently in patients treated with ACTOS than in placebo-treated patients and appears to be dose related (see ADVERSE REACTIONS). In postmarketing experience, reports of initiation or worsening of edema have been received.

Weight Gain: Dose related weight gain was seen with ACTOS alone and in combination with other hypoglycemic agents (Table 6). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Table 6 Weight Changes (kg) from Baseline during Double-Blind Clinical Trials with ACTOS

		Control Group (Placebo)	ACTOS 15 mg	ACTOS 30 mg	ACTOS 45 mg
		Median (25th/75th percentile)	Median (25th/75th percentile)	Median (25th/75th percentile)	Median (25th/75th percentile)
Monotherapy		-1.4 (-2.7/0.0) n=256	0.9 (-0.5/3.4) n=79	1.0 (-0.9/3.4) n=188	2.6 (0.2/5.4) n=79
Combination Therapy	Sulfonylurea	-0.5 (-1.8/0.7) n=187	2.0 (0.2/3.2) n=183	3.1 (1.1/5.4) n=528	4.1 (1.8/7.3) n=333
	Metformin	-1.4 (-3.2/0.3) n=160	N/A	0.9 (-0.3/3.2) n=567	1.8 (-0.9/5.0) n=407
	Insulin	0.2 (-1.4/1.4) n=182	2.3 (0.5/4.3) n=190	3.3 (0.9/6.3) n=522	4.1 (1.4/6.8) n=338

Note: Trial durations of 16 to 26 weeks

Ovulation: Therapy with ACTOS, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking ACTOS. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been investigated in clinical studies so the frequency of this occurrence is not known.

Hematologic: ACTOS may cause decreases in hemoglobin and hematocrit. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in patients treated with ACTOS. These changes primarily occurred within the first 4 to 12 weeks of therapy and remained relatively constant thereafter. These changes may be related to increased plasma volume and have rarely been associated with any significant hematologic clinical effects (see ADVERSE REACTIONS, Laboratory Abnormalities).

Hepatic Effects: In pre-approval clinical studies worldwide, over 4500 subjects were treated with ACTOS. In U.S. clinical studies, over 4700 patients with type 2 diabetes received ACTOS. There was no evidence of drug-induced hepatotoxicity or elevation of ALT levels in the clinical studies.

During pre-approval placebo-controlled clinical trials in the U.S., a total of 4 of 1526 (0.26%) patients treated with ACTOS and 2 of 793 (0.25%) placebo-treated patients had ALT values ≥ 3 times the upper limit of normal. The ALT elevations in patients treated with ACTOS were reversible and were not clearly related to therapy with ACTOS.

In postmarketing experience with ACTOS, reports of hepatitis and of hepatic enzyme elevations to 3 or more times the upper limit of normal have been received. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established.

Pioglitazone is structurally related to troglitazone, a thiazolidinedione no longer marketed in the United States, which was associated with idiosyncratic hepatotoxicity and cases of liver failure, liver transplants and death during postmarketing clinical use. In pre-approval controlled clinical trials in patients with type 2 diabetes, troglitazone was more frequently associated with clinically significant elevations of hepatic enzymes (ALT > 3 times the upper limit of normal) compared to placebo, and cases of reversible jaundice were reported.

Pending the availability of the results of additional large, long-term controlled clinical trials and additional postmarketing safety data, it is recommended that patients treated with ACTOS undergo periodic monitoring of liver enzymes.

Serum ALT (alanine aminotransferase) levels should be evaluated prior to the initiation of therapy with ACTOS in all patients and periodically thereafter per the clinical judgment of the health care professional. Liver function tests should also be obtained for patients if symptoms suggestive of hepatic dysfunction occur, e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine. The decision whether to continue the patient on therapy with ACTOS should be guided by clinical judgment pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

Therapy with ACTOS should not be initiated if the patient exhibits clinical evidence of active liver disease or the ALT levels exceed 2.5 times the upper limit of normal. Patients with mildly elevated liver enzymes (ALT levels at 1 to 2.5 times the upper limit of normal) at baseline or any time during therapy with ACTOS should be evaluated to determine the cause of the liver enzyme elevation. Initiation or continuation of therapy with ACTOS in patients with mildly elevated liver enzymes should proceed with caution and include appropriate clinical follow-up which may include more frequent liver enzyme monitoring. If serum transaminase levels are increased (ALT > 2.5 times the upper limit of normal), liver function tests should be evaluated more frequently until the levels return to normal or pretreatment values. If ALT levels exceed 3 times the upper limit of normal, the test should be repeated as soon as possible. If ALT levels remain > 3 times the upper limit of normal or if the patient is jaundiced, ACTOS therapy should be discontinued.

There are no data available to evaluate the safety of ACTOS in patients who experienced liver abnormalities, hepatic dysfunction, or jaundice while on troglitazone. ACTOS should not be used in patients who experienced jaundice while taking troglitazone.

Laboratory Tests
FPG and HbA_{1c} measurements should be performed periodically to monitor glycemic control and the therapeutic response to ACTOS.

Liver enzyme monitoring is recommended prior to initiation of therapy with ACTOS in all patients and periodically thereafter per the clinical judgment of the health care professional (see PRECAUTIONS, General, Hepatic Effects and ADVERSE REACTIONS, Serum Transaminase Levels).

Information for Patients
It is important to instruct patients to adhere to dietary instructions and to have blood glucose and glycosylated hemoglobin tested regularly. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be reminded to seek medical advice promptly.

Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on ACTOS should immediately report these symptoms to their physician.

Patients should be told that blood tests for liver function will be performed prior to the start of therapy and periodically thereafter per the clinical judgment of the health care professional. Patients should be told to seek immediate medical advice for unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine.

Patients should be told to take ACTOS once daily. ACTOS can be taken with or without meals. If a dose is missed on one day, the dose should not be doubled the following day.

When using combination therapy with insulin or oral hypoglycemic agents, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

Therapy with ACTOS, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking ACTOS. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been investigated in clinical studies so the frequency of this occurrence is not known.

Drug Interactions
In vivo drug-drug interaction studies have suggested that pioglitazone may be a weak inducer of CYP 450 isoform 3A4 substrate (see CLINICAL PHARMACOLOGY, Metabolism and Drug-Drug Interactions).

Carcinogenesis, Mutagenesis, Impairment of Fertility
A two-year carcinogenicity study was conducted in male and female rats at oral doses up to 63 mg/kg (approximately 14 times the maximum recommended human oral dose of 45 mg based on mg/m^2). Drug-induced tumors were not

observed in any organ except for the urinary bladder. Benign and/or malignant transitional cell neoplasms were observed in male rats at 4 mg/kg/day and above (approximately equal to the maximum recommended human oral dose based on mg/m^2). A two-year carcinogenicity study was conducted in male and female mice at oral doses up to 100 mg/kg/day (approximately 11 times the maximum recommended human oral dose based on mg/m^2). No drug-induced tumors were observed in any organ. Urinary tract tumors have been reported in rodents taking experimental drugs with dual PPAR α/γ activity; however, ACTOS is a selective agonist for PPARγ.

During prospective evaluation of urinary cytology involving more than 1800 patients receiving ACTOS in clinical trials up to one year in duration, no new cases of bladder tumors were identified. Occasionally, abnormal urinary cytology results indicating possible malignancy were observed in both patients treated with ACTOS (0.72%) and patients treated with placebo (0.88%).

Pioglitazone HCl was not mutagenic in a battery of genetic toxicology studies, including the Ames bacterial assay, a mammalian cell forward gene mutation assay (CHO/HPRT and AS52/XPRT), an in vitro cytogenetics assay using CHL cells, an unscheduled DNA synthesis assay, and an in vivo micronucleus assay.

No adverse effects upon fertility were observed in male and female rats at oral doses up to 40 mg/kg pioglitazone HCl daily prior to and throughout mating and gestation (approximately 9 times the maximum recommended human oral dose based on mg/m^2).

Animal Toxicology

Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with pioglitazone HCl (approximately 11, 1, and 2 times the maximum recommended human oral dose for mice, rats, and dogs, respectively, based on mg/m^2). In a one-year rat study, drug-related early death due to apparent heart dysfunction occurred at an oral dose of 160 mg/kg/day (approximately 35 times the maximum recommended human oral dose based on mg/m^2). Heart enlargement was seen in a 13-week study in monkeys at oral doses of 8.9 mg/kg and above (approximately 4 times the maximum recommended human oral dose based on mg/m^2), but not in a 52-week study at oral doses up to 32 mg/kg (approximately 13 times the maximum recommended human oral dose based on mg/m^2).

Pregnancy

Pregnancy Category C. Pioglitazone was not teratogenic in rats at oral doses up to 80 mg/kg or in rabbits given up to 160 mg/kg during organogenesis (approximately 17 and 40 times the maximum recommended human oral dose based on mg/m^2, respectively). Delayed parturition and embryotoxicity (as evidenced by increased postimplantation losses, delayed development and reduced fetal weights) were observed in rats at oral doses of 40 mg/kg/day and above (approximately 10 times the maximum recommended human oral dose based on mg/m^2). No functional or behavioral toxicity was observed in offspring of rats. In rabbits, embryotoxicity was observed at an oral dose of 160 mg/kg (approximately 40 times the maximum recommended human oral dose based on mg/m^2). Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats at oral doses of 10 mg/kg and above during late gestation and lactation periods (approximately 2 times the maximum recommended human oral dose based on mg/m^2).

There are no adequate and well-controlled studies in pregnant women. ACTOS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies, as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers

Pioglitazone is secreted in the milk of lactating rats. It is not known whether ACTOS is secreted in human milk. Because many drugs are excreted in human milk, ACTOS should not be administered to a breast-feeding woman.

Pediatric Use

Safety and effectiveness of ACTOS in pediatric patients have not been established.

Elderly Use

Approximately 500 patients in placebo-controlled clinical trials of ACTOS were 65 and over. No significant differences in effectiveness and safety were observed between these patients and younger patients.

ADVERSE REACTIONS

In worldwide clinical trials, over 5900 patients with type 2 diabetes have been treated with ACTOS. In U.S. clinical trials, over 4700 patients have received ACTOS, over 3300 patients have been treated for 6 months or longer, and over 450 patients for one year or longer.

The overall incidence and types of adverse events reported in placebo-controlled clinical trials of ACTOS monotherapy at doses of 7.5 mg, 15 mg, 30 mg, or 45 mg once daily are shown in Table 7.

Table 7 Placebo-Controlled Clinical Studies of ACTOS Monotherapy: Adverse Events Reported at a Frequency ≥ 5% of Patients Treated with ACTOS

(% of Patients)		
	Placebo N=259	ACTOS N=606
Upper Respiratory Tract Infection	8.5	13.2
Headache	6.9	9.1
Sinusitis	4.6	6.3
Myalgia	2.7	5.4
Tooth Disorder	2.3	5.3
Diabetes Mellitus Aggravated	8.1	5.1
Pharyngitis	0.8	5.1

For most clinical adverse events the incidence was similar for groups treated with ACTOS monotherapy and those treated in combination with sulfonylureas, metformin, and insulin. There was an increase in the occurrence of edema in the patients treated with ACTOS and insulin compared to insulin alone.

In a 16-week, placebo-controlled ACTOS plus insulin trial (n=379), 10 patients treated with ACTOS plus insulin developed dyspnea and also, at some point during their therapy, developed either weight change or edema. Seven of these 10 patients received diuretics to treat these symptoms. This was not reported in the insulin plus placebo group.

The incidence of withdrawals from placebo-controlled clinical trials due to an adverse event other than hyperglycemia was similar for patients treated with placebo (2.8%) or ACTOS (3.3%).

In controlled combination therapy studies with either a sulfonylurea or insulin, mild to moderate hypoglycemia, which appears to be dose related, was reported (see PRECAUTIONS, General, Hypoglycemia and DOSAGE and ADMINISTRATION, Combination Therapy).

In U.S. double-blind studies, anemia was reported in ≤ 2% of patients treated with ACTOS plus sulfonylurea, metformin or insulin (see PRECAUTIONS, General, Hematologic).

In monotherapy studies, edema was reported for 4.8% of patients treated with ACTOS versus 1.2% of placebo-treated patients. In combination therapy studies, edema was reported for 7.2% of patients treated with ACTOS and sulfonylureas compared to 2.1% of patients on sulfonylureas alone. In combination therapy studies with metformin, edema was reported in 6.0% of patients on combination therapy compared to 2.5% of patients on metformin alone. In combination therapy studies with insulin, edema was reported in 15.3% of patients on combination therapy compared to 7.0% of patients on insulin alone. Most of these events were considered mild or moderate in intensity (see PRECAUTIONS, General, Edema).

In one 16-week clinical trial of insulin plus ACTOS combination therapy, more patients developed congestive heart failure on combination therapy (1.1%) compared to none on insulin alone (see WARNINGS, Cardiac Failure and Other Cardiac Effects).

Laboratory Abnormalities

Hematologic: ACTOS may cause decreases in hemoglobin and hematocrit. The fall in hemoglobin and hematocrit with ACTOS appears to be dose related. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in patients treated with ACTOS. These changes generally occurred within the first 4 to 12 weeks of therapy and remained relatively stable thereafter. These changes may be related to increased plasma volume associated with ACTOS therapy and have rarely been associated with any significant hematologic clinical effects.

Serum Transaminase Levels: During all clinical studies in the U.S., 14 of 4780 (0.30%) patients treated with ACTOS had ALT values ≥ 3 times the upper limit of normal during treatment. All patients with follow-up values had reversible elevations in ALT. In the population of patients treated with ACTOS, mean values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline. Fewer than 0.9% of patients treated with ACTOS were withdrawn from clinical trials in the U.S. due to abnormal liver function tests.

In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure (see PRECAUTIONS, Hepatic Effects).

CPK Levels: During required laboratory testing in clinical trials, sporadic, transient elevations in creatine phosphokinase levels (CPK) were observed. An isolated elevation to greater than 10 times the upper limit of normal was noted in 9 patients (values of 2150 to 11400 IU/L). Six of these patients continued to receive ACTOS, two patients had completed receiving study medication at the time of the elevated value and one patient discontinued study medication due to the elevation. These elevations resolved without any apparent clinical sequelae. The relationship of these events to ACTOS therapy is unknown.

OVERDOSAGE

During controlled clinical trials, one case of overdose with ACTOS was reported. A male patient took 120 mg per day for four days, then 180 mg per day for seven days. The patient denied any clinical symptoms during this period.

In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

DOSAGE AND ADMINISTRATION

ACTOS should be taken once daily without regard to meals.

The management of antidiabetic therapy should be individualized. Ideally, the response to therapy should be evaluated using HbA_{1c} which is a better indicator of long-term glycemic control than FPG alone. HbA_{1c} reflects glycemia over the past two to three months. In clinical use, it is recommended that patients be treated with ACTOS for a period of time adequate to evaluate change in HbA_{1c} (three months) unless glycemic control deteriorates.

Monotherapy

ACTOS monotherapy in patients not adequately controlled with diet and exercise may be initiated at 15 mg or 30 mg once daily. For patients who respond inadequately to the initial dose of ACTOS, the dose can be increased in increments up to 45 mg once daily. For patients not responding adequately to monotherapy, combination therapy should be considered.

Combination Therapy

Sulfonylureas: ACTOS in combination with a sulfonylurea may be initiated at 15 mg or 30 mg once daily. The current sulfonylurea dose can be continued upon initiation of ACTOS therapy. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased.

Metformin: ACTOS in combination with metformin may be initiated at 15 mg or 30 mg once daily. The current metformin dose can be continued upon initiation of ACTOS therapy. It is unlikely that the dose of metformin will require adjustment due to hypoglycemia during combination therapy with ACTOS.

Insulin: ACTOS in combination with insulin may be initiated at 15 mg or 30 mg once daily. The current insulin dose can be continued upon initiation of ACTOS therapy. In patients receiving ACTOS and insulin, the insulin dose can be decreased by 10% to 25% if the patient reports hypoglycemia or if plasma glucose concentrations decrease to less than 100 mg/dL. Further adjustments should be individualized based on glucose-lowering response.

Maximum Recommended Dose

The dose of ACTOS should not exceed 45 mg once daily in monotherapy or in combination with sulfonylurea, metformin or insulin.

Dose adjustment in patients with renal insufficiency is not recommended (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism).

Therapy with ACTOS should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT greater than 2.5 times the upper limit of normal) at start of therapy (see PRECAUTIONS, General, Hepatic Effects and CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency). Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with ACTOS and periodically thereafter (see PRECAUTIONS, General, Hepatic Effects).

There are no data on the use of ACTOS in patients under 18 years of age; therefore, use of ACTOS in pediatric patients is not recommended.

No data are available on the use of ACTOS in combination with another thiazolidinedione.

HOW SUPPLIED

ACTOS is available in 15 mg, 30 mg, and 45 mg tablets as follows:

15 mg Tablet: white to off-white, round, convex, non-scored tablet with "ACTOS" on one side, and "15" on the other, available in:
NDC 64764-151-04 Bottles of 30
NDC 64764-151-05 Bottles of 90
NDC 64764-151-06 Bottles of 500

30 mg Tablet: white to off-white, round, flat, non-scored tablet with "ACTOS" on one side, and "30" on the other, available in:
NDC 64764-301-14 Bottles of 30
NDC 64764-301-15 Bottles of 90
NDC 64764-301-16 Bottles of 500

45 mg Tablet: white to off-white, round, flat, non-scored tablet with "ACTOS" on one side, and "45" on the other, available in:
NDC 64764-451-24 Bottles of 30
NDC 64764-451-25 Bottles of 90
NDC 64764-451-26 Bottles of 500

STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed, and protect from moisture and humidity.

Rx only

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Osaka, Japan

Marketed by:
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